DEPARTMENT OF HEALTH & HUMAN SERVICES 9176d
New York District

Food & Drug Administration
158-15 Liberty Avenue
Jamaica, NY 11433

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Gordon Proctor
President and CEO
Sanofi-Synthelabo, Inc.
90 Park Avenue
New York, NY 10016

September 21, 2001

Ref: NYK-2001-126

Dear Mr. Proctor:

During the period August 3 through 7, 2001, an investigator from the New York District Office conducted an inspection of your firm located at the above address to determine your firm's compliance with the Postmarketing Adverse Drug Experience (PADE) reporting requirements of Section 505(k) of the Federal Food, Drug, and Cosmetic Act ("the Act"), and Title 21, *Code of Federal Regulations* (CFR), Part 314.80.

Based on our review of the inspection report, we conclude that your firm failed to comply with Section 505(k)(1) of the Act and 21 CFR 314.80, which require the reporting of data relating to clinical experience for drugs for which an approval of an application filed under 505(b) is in effect. Deviations from the PADE regulation include the following:

Your firm did not submit a number of serious and unexpected adverse drug experience reports to the Food and Drug Administration ("FDA") within 15 calendar days of initial receipt of the information as required by 21 CFR 314.80(c)(1)(i). For example, our investigator observed that 42 of 72 initial PADE reports for your drug Plavix (NDA 20-839), received from foreign sources on or after February 14, 2001, were not submitted on time. These reports include, but are not limited to:

Mfr. Control No.	Date Received by Mfr.	Date Sent to FDA
N129333	May 28,2001	July 9, 2001
N127613	January 5, 2001	April 18, 2001
N129292	May 29, 2001	July 9, 2001
N127604	February 21, 2001	July 9, 2001
N129282	May 29, 2001	July 9, 2001
N129502	June 6, 2001	July 9, 2001

N129088	May 14, 2001	July 9, 2001
N129500	May 31, 2001	July 9, 2001
N129077	May 15, 2001	July 10, 2001
N129412	June 4, 2001	July 9, 2001
N128849	May 2, 2001	July 9, 2001
N129397	May 31, 2001	July 9, 2001
N127816	March 7, 2001	April 3, 2001
N129338	May 29, 2001	July 9, 2001
N127737	March 2, 2001	March 27, 2001
N129337	May 29, 2001	July 9, 2001
N127373	February 19, 2001	March 13, 2001
N127347	February 16, 2001	July 9, 2001

Neither the above list of deviations nor the Form FDA 483 "Inspectional Observations", which was presented to and discussed with Dr. David Goldsmith, Vice President Drug Safety Surveillance, at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and its regulations. The FDA expects drug manufacturers to establish reasonable mechanisms to assure that their foreign affiliates and corporate units rapidly transmit information to expedite reporting of serious and unlabeled adverse drug experiences to the FDA.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include but are not limited to seizure and/or injunction. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

We acknowledge receipt of a letter dated August 29, 2001, from Drs. Goldsmith and Salliere of your firm, which sets forth your firm's corrective action plan in regard to these deviations. We need, however, to have the following items clarified:

- Your firm's letter states that "half of late reports were received from regulatory agencies other than the FDA and were complicated by differences in the labeling among various countries." Does your firm use current approved U.S. labeling when evaluating adverse drug events for submission to FDA? Also please clarify how the source of event data specifically affects your firm's ability to submit reports in a timely manner.

- Your firm's letter identified "priority conflicts" and a "limitation in the Corporate tracking system" that inhibited your discovery of the reporting problem in a more timely manner. Please identify to us what these "priority conflicts" and "limitation" consisted of and how you plan to address these problems.

- Your firm's letter indicates that ADE reporting for Plavix was particularly affected by "priority conflicts" and "tracking limitations." What are the factors associated with ADE reporting for Plavix that made Plavix particularly affected by priority conflicts and tracking limitations? Please explain how your firm has addressed or will addressed those factors in order to make your reporting timely.

- Your firm states that as a preventive measure, Corporate will be notified of any case arriving later than 12 days after the clock starts. That measure does not appear to us as serving a preventive role. Are there any procedures for you to be notified of open cases which have not been received within a certain period, such as by day 12 or earlier? Are reports from the tracking system now available to the U.S. affiliate staff, so that they can be alerted to open cases that have not yet been received, and be informed of the original receipt date of the information?

We request that you reply in writing within 15 working days of receipt of this letter. Your reply should be sent to the Food and Drug Administration, 158-15 Liberty Avenue, Jamaica, NY 11433, Attn: Bruce A. Goldwitz, Compliance Officer. If you have any questions or concerns, you can contact Mr. Goldwitz at (718) 340-7000 ext. 5582.

Sincerely,

Jerome G. Woyshner
District Director

Enclosure: Form FDA 483 dated August 7, 2001